REMARKS

I. Status of the Application and Claims:

Claims 1-29 are pending in the application. Claims 8, 10-12, 14-19, and 25-27 have been withdrawn from consideration. Claims 1-7, 9, 13, 20-24, 28, and 29 have been examined on the merits and stand rejected.

Applicants acknowledge that the pending restriction requirement has been made final. Office action, page 3.

Applicants have amended claims 1, 2, 3, 13, and 16-29 solely to more clearly recite their invention. Withdrawn claims 16-19, and 25-27 have been amended to correct errors in their dependency introduced by the renumbering of the claims by the Office. *See* Office action mailed January 2, 2003, page 2. Pending claims 20, 22-24, and 28 have also been amended to correct their dependency in view of the same renumbering of the claims.

In addition, Applicants have amended claims 1-3 13, 21-23, and 29. Support for the amendments is found in the specification at, for example, page 3, lines 1-3, and page 7, lines 22-24. No new matter has been entered by the amendments.

II. The Claims Are Definite and Unambiguous

The Office rejects claims 1-7, 9, 13, 22-24, 28, and 29 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as their invention. Office action, page 3. Applicants traverse the rejection.

The Office objects to the term "modification" in claim 1 "because artisan would not know what other, if any, features are to accompany the mutation to constitute the 'modification.'" *Id.* Applicants have rewritten the claims to remove reference to a

modification of the heterologous G protein-coupled receptor. Accordingly, that ground for rejection is moot.

The office has also rejected claims 1, 4-7, 9, 13, 20, 21, 24, 28, and 29 based on the requirement that the receptor has "an improved functional response" because the specification allegedly does not teach skilled artisan how to identify which properties of the receptor are considered by applicants to be "functions" and which are not. *Id.* Applicants have canceled the language from the claims and replaced it with "the mutation improving the function of said heterologous G protein-coupled receptor by causing it to couple more efficiently with a heterotrimeric G protein." In view of the amendment, Applicants submit that the rejection based on that ground is moot.

With respect to claim 22, the Office contends that "the modification" lacks antecedent basis. Applicants have amended claim 22 to replace "the modification" with "deletion," which is introduced in a dependent claim 21. That ground of rejection is moot.

Finally, claim 29 is rejected based on the language "the deletion is IC3Δ." *Id.*, page 4. In view of the teaching of the specification at page 7, lines 19-24, Applicants submit that one of skill in the art would readily understand the meaning of "IC3Δ." Accordingly, claim 29 is not ambiguous and Applicants request that the Office reconsider and withdraw the rejection.

In view of these remarks, Applicants request that the office reconsider and withdraw the rejections under section 112, second paragraph.

III. The Cited References Do Not Anticipate the Claims

A. Strader

Claims 1, 3-7, 9, 21, and 29 have been rejected under 35 U.S.C. § 102(b) as allegedly unpatentable over PCT application WO 96/00739 to Strader *et al.* ("Strader"). According to the Office, "Strader disclose an assay using yeast cells (pg9) wherein the ratM3 muscarinic acid receptor is mutated in the third intracellular domain by deletion of at least one amino acid (pge 13, L24-30 resulting in the enhanced function of the receptor in a cell based assay, i.e. the receptor binds the ligand with high affinity in the absence of G-protein (pg 13, L3-L14)." Office action, page 5. The Office also notes that "Strader teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G protein." *Id.* Applicants traverse the rejection.

As amended, the rejected claims recite a mutated heterologous G protein coupled receptor wherein "said mutation improve[es] the function of said heterologous G protein-coupled receptor by causing it to couple more efficiently with a heterotrimeric G protein . . . ." The mutation described by Strader, and relied on by the Office in rejecting the claims has exactly the opposite effect. As Strader says, "the modified receptor does not couple well to G proteins . . . ." Strader, page 13, lines 10 and 11. In other words, the mutations described by Strader are not mutations that cause a G protein-coupled receptor to couple more efficiently with a heterotrimeric G protein.

Anticipation requires that a single prior art reference teach each and every element of the claimed invention. Strader does not do so. Nor does Strader suggest

the recited mutations Thus, Applicants request that the Office reconsider and withdraw the rejection.

B. Sledziewski

The Office rejects claims 1 and 20 under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,576,210 to Sledziewski *et al.* ("Sledziewski"). Office action, page 5. The office contends that "Sledziewski teach a yeast cell comprising a nucleic acid sequence encoding the modified heterologous GPCR, wherein the modification comprises a mutation in an intracellular domain of the GPCR and results in an improved functional response in a cell based assay as compared to wild type . . . ." *Id.* As support for this conclusion, the Office cites to the abstract and to column 3 of the reference. Applicants traverse.

Sledziewski describes hybrid mammalian/yeast G protein-coupled receptors. As the Abstract of Sledziewski indicates, "the receptor is comprised mammalian G protein-coupled receptors having at least one domain other than the ligand-binding domain and replaced with a corresponding domain of a yeast G protein-coupled receptor." Nothing in the abstract, nor in column 3 of the reference, teaches (or suggests) introducing a mutation "in an intracellular domain of the G protein-coupled receptor," much less a mutation "improving the function of said heterologous G protein-coupled receptor by causing it to couple more efficiently with a heterotrimeric G protein."

Sledziewski, therefore, does not teach (or suggest) each and every element of claims 1 and 20. For that reason, Applicants request that the Office reconsider and withdraw the rejection.

C. **Fowlkes**

Claims 1-7, 20-24, 28, and 29 stand rejected under 35 U.S.C. §§ 102(a) and (e) as allegedly being anticipated by U.S. Patent No. 5,789,184 to Fowlkes *et al.* ("Fowlkes"). Office action, page 5. According to the Office, "Fowlkes disclose yeast cells comprising a nucleic acid encoding a GPCR (e.g. a muscarinic receptor, that may be mutated, Col 26, L19-25) that has been modified as a matter of routine optimization of operating parameters, i.e. such that it is improved in its functions in a cell based assay as compared to wild type, (col. 15, L29-L63), wherein the modification comprises a deletion is [sic] in one of the loops of the GPCR (col 15, L57)." The Office contends that "[o]ne of ordinary skill in the art would understand from the teachings of col. 15 that the reference to 'loops' at line 57 necessarily includes the third intracellular loop because it is only one of six loops." The Office also asserts that " the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells, see col. 10, L27-44." *Id.*, page 6. Applicants traverse the rejection.

Applicants disagree with the Office's interpretation of Fowlkes. Looking at the section of the reference cited and relied on by the Office in making the rejection, col. 26, lines 19-25, Applicants agree in that passage Fowlkes describes various G protein-coupled receptors and that "receptor" as used "encompasses both naturally occurring and mutant receptors." However, neither that passage, nor the cited passage at col. 15, lines 29-63 describe introducing mutations into a heterologous G protein-coupled receptor to improve its function in a cell-based assay, as the Office contends. Moreover, those sections do not teach (or suggest) introducing a mutation "in an intracellular domain of the G protein-coupled receptor," much less a mutation "improving

the function of said heterologous G protein-coupled receptor by causing it to couple more efficiently with a heterotrimeric G protein." Instead, col. 15 merely describes various "conservative modifications" that may or may not be introduced into a "PSP surrogate," which may or may not be a G protein-coupled receptor. Even if this were interpreted as teaching a heterologous G protein-coupled receptor having a mutation in an intracellular domain, which Applicants do not concede, the reference does not teach that such a mutation would cause the mutated G protein-coupled receptor to couple more efficiently with a heterotrimeric G protein.

The Office also cites to col. 10, lines 27-44. Nothing in this section, contrary to the Office's assertion, teaches or suggest "the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells . . . ." Instead, this section mentions the undesirable growth arrest consequence of activating the pheromone response pathway and identifies three ways of overcoming that problem. *See* col. 15, lines 36-43. None of those three ways involve introducing mutation recited in the claims into a heterologous G protein-coupled receptor.

Hence, Fowlkes does not teach (or suggest) each and every limitation of the rejected claims. Because it fails to do so, the Office should reconsider and withdraw the rejection.

IV. The Cited References Do Not Render the Claims Obvious

A. Sledziewski and King

Claim 2 has been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sledziewski in view of PCT application WO 92/05244 to King *et al.* ("King"). Office action, page 6. Applicants traverse the rejection because the references do not render

the claims *prima facie* obvious in that they fail to teach or suggest all of the limitations of the rejected claim.

Applicants have discussed the teaching of Sledziewski and its deficiencies. King is cited as teaching an assay where the effect of an agonist would be to induce HIS3, which is used to produce agonist-induced growth of cells. *Id.*, page 7. According to the Office, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to use HIS3 as a reporter gene as taught by King in the assays taught by both King and Sledziewski wherein the GPCR comprises a modification as taught by Sledziewski." *Id.*

The teaching of King, however, does not cure the deficiency in the teaching of Sledziewski, which Applicants have noted above with respect to the rejection based on lack of novelty. The combination of Sledziewski and King, therefore, does not teach or suggest all of the limitations of the rejected claim. For that reason, claim 2 is not *prima facie* obvious over that combination of references. Applicants request that the Office reconsider and withdraw the rejection.

In addition, one of skill in the art would not have been motivated to combine the reference, nor have a reasonable teaching of success in view of the teaching of Strader. As the Office notes, "Strader teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G protein." Office action, page 5. Applicants submit that teaching is further evidence showing the unobviousness of the claims over the cited references.

B. **Sledziewski and Bonner**

The Office rejects claim 9 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sledziewski in view of Bonner *et al.*, Science, 237:527-537 (1987) ("Bonner"). Office action, page 7. Applicants traverse the rejection because the references do not render the claims *prima facie* obvious in that they fail to teach or suggest all of the limitations of the rejected claim.

Applicants have discussed the teaching of Sledziewski and its deficiencies. Bonner is only cited for its teaching of the rat M3 muscarinic receptor. *Id.* The teaching of Bonner does not cure the deficiency in the teaching of Sledziewski, which Applicants have noted above. Therefore, the combination of Sledziewski and Bonner does not teach or suggest all of the limitations of claim 9. For that reason, claim 9 is not *prima facie* obvious over that combination of references. Applicants request that the Office reconsider and withdraw the rejection.

In addition, one of skill in the art would not have been motivated to combine the reference, nor have a reasonable teaching of success in view of the teaching of Strader. As the Office notes, "Strader teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G protein." Office action, page 5. Applicants submit that teaching is further evidence showing the unobviousness of the claims over the cited references.

C. **Fowlkes and Bonner**

Claim 9 is also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Fowlkes in view of Bonner. Office action, page 8. Applicants traverse the rejection

because the references do not render the claims *prima facie* obvious in that they fail to teach or suggest all of the limitations of the rejected claim.

Applicants have discussed the teaching of Fowlkes and its deficiencies. Bonner is cited for its teaching of the rat M3 muscarinic receptor. As in the case of the combination of Sledziewski and Bonner, the combination of Fowlkes and Bonner does not cure the deficiency in the teaching of the primary reference Fowlkes. The combination of Fowlkes and Bonner, therefore, does not teach or suggest all of the limitations of the rejected claim. For that reason, claim 9 is not *prima facie* obvious over that combination of references. Applicants request that the Office reconsider and withdraw the rejection.

In addition, one of skill in the art would not have been motivated to combine the reference, nor have a reasonable teaching of success in view of the teaching of Strader. As the Office notes, "Strader teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G protein." Office action, page 5. Applicants submit that teaching is further evidence showing the unobviousness of the claims over the cited references.

V. The Specification Enables the Full Scope of Claim 13

Claims 13 has been rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while been enabling for a modification that results in a 44 amino acid third intracellular loop comprising the 22 residues proximal to the 5th and 6th transmembrane domains," allegedly "does not reasonably provide enablement for all other modifications resulting in a 44 amino acid third intracellular loop." Office action, page 9. Applicants traverse.

It appears the Office is asserting that the specification, combined with the knowledge available in the art as of Applicants' filing date, would not permit one to make deletions in the third intracellular loop of a heterologous G protein-coupled receptor wherein 44 amino acids remain of that intracellular loop without undue experimentation. At the time of Applicants' invention, the level of skill in the art was well developed and methods for introducing deletions into known DNA sequences were readily available to the skilled artisan. The Office appears to believe that because the claims cover a broad range of different deletions, one could not make those mutations without undue experimentation. What the Office fails to explain, however, is why the methods known in the art and readily used to make one mutation could not be used to make others. In other words, if the methodology works for one mutation it should work for all. The Office cannot merely surmise that the method(s) would not work. It must provide evidence they would not work. Here, the Office has failed to supply the required evidence. For that reason, the Office should reconsider and withdraw the rejection.

The Office analogizes claim 13 to the functional claim found deficient in *In re Hyatt*, 708 F.2d 712 (Fed. Cir. 1983). That characterization, Applicants submit, is erroneous. *Hyatt* involved a claim drafted using only functional language. The court held that such a claim was impermissibly abroad because it read on any means capable of achieving the recited function. That is not the case here. Claim 13 is not written in functional language. The language is structural. Accordingly, the holding in *Hyatt* has no bearing on the enablement of claim 13.

For these reasons, Applicants submit that claim 13 is enabled by the specification. Thus, they request that the Office reconsider and withdraw this rejection

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: July 12, 2004

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